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EXAMINER	
LIU, SUE XU	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/776,180	BEAUREGARD ET AL.	
	Examiner	Art Unit	
	Sue Liu	1639	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *02 October 2007*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-3,11-17 and 22-30* is/are pending in the application.

4a) Of the above claim(s) *14-16 and 27-30* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-3, 11-13, 17 and 22-26* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Continued Examination Under 37 CFR 1.114

1. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 10/2/07 has been entered.

Claim Status

2. Claims 4-10 and 18-21 have been canceled as filed on 10/2/07.

Claims 22-30 have been added as filed on 10/2/07.

Claims 1-3, 11-17 and 22-30 are currently pending.

Claims 14-16 and 27-30 have been withdrawn.

Claims 1-3, 11-13, 17 and 22-26 are being examined in this application.

Election/Restrictions

3. Applicant's election without traverse of Group I (Claims 1-10) in the reply filed on 10/27/2005 is as previously acknowledged. The newly added claims 22-30 are drawn to the Group I invention.

4. Upon further consideration, the previously set forth restriction among the claims of Group I invention and the instant claims 11-13 and 17 are withdrawn, and the instant claims 1-3, 11-13, 17 and 22-30 are grouped together with the Group I invention.

5. Applicant also elected without traverse of the following species in the Reply filed on 10/27/05 (Reply, p.5, para 3):

A.) Thermostable DNA polymerase, and more particularly, *Thermococcus litoralis*;

B.) 0.05 to 1.0 molar for molar concentration;

C.) 1-propanol;

D.) Transition;

E.) 1 to 10 mutations per nucleotides sequence having one hundred (100) nucleic acids.

Accordingly, the non-elected species are withdrawn from the corresponding claims. Claims 27-30 are withdrawn due to non-elected species (e.g. the non-elected "*Thermus aquaticus*" polymerase).

Priority

6. This application claims priority to provisional application 60/446,518 filed on 2/12/2003.

7. Applicant's claim for the benefit of a prior-filed application under 35 U.S.C. 119(e) or under 35 U.S.C. 120, 121, or 365(c) is acknowledged. Applicant has not complied with one or more conditions for receiving the benefit of an earlier filing date under 35 U.S.C. 119(e) or under 35 U.S.C. 120, 121, or 365(c) as follows:

The later-filed application must be an application for a patent for an invention which is also disclosed in the prior application (the parent or original nonprovisional application or

provisional application). The disclosure of the invention in the parent application and in the later-filed application must be sufficient to comply with the requirements of the first paragraph of 35 U.S.C. 112. See *Transco Products, Inc. v. Performance Contracting, Inc.*, 38 F.3d 551, 32 USPQ2d 1077 (Fed. Cir. 1994).

The disclosure of the prior-filed application, Application No. 60/446518, fails to provide adequate support or enablement in the manner provided by the first paragraph of 35 U.S.C. 112 for one or more claims of this application.

The instant claims have been amended (as filed on 10/2/07) to recite " DNA template of between 50 and 50 000 base pair", which range of DNA template length does not appear to have support in the provisional application, 60/446518. The said subject matter of the instant claims would not obtain the priority date of the provisional application.

Thus, the effective filing date of the said subject matter is 2/12/2004.

Specification

Sequence Rule Compliance

8. "In order to expedite the processing of applications, minor errors pertaining to compliance with the sequence rules may be handled with the first Office action." See MPEP 2427.01.

9. This application contains sequence disclosures that are encompassed by the definitions for nucleotide and/or amino acid sequences set forth in 37 CFR § 1.821(a)(1) and (a)(2). However, this application fails to comply with the requirements of 37 CFR §§ 1.821 through 1.825 for the reason(s) below:

The instant disclosure recites lists of sequences in the drawings (see Figure 6), which are not identified by their corresponding SEQ ID Nos in the "BRIEF DESCRIPTION OF THE FIGURES AND TABLES" of the instant specification. Applicants are requested to amend the instant specification and claims accordingly.

In order to be fully responsive to the instant office action, applicants are requested to fully comply with the Sequence Rule.

Claim Rejections Maintained

Claim Rejections - 35 USC § 112

10. The following is a quotation of the **first paragraph of 35 U.S.C. 112**:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Scope of Enablement Rejection

11. Claims 1-3 and 22-26 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for 1-propanol used in PCR reaction with thermo polymerase, Vent$_r$® with DNA template of less than or equal to 2.8kb (such as MB-1 His gene) to generate mutations in DNA with length less than or equal to 0.8kb in the presence of less than 8% 1-propanol, does not reasonably provide enablement for any other *Thermococcus litoralis* DNA polymerase, any other DNA template with any other length, any other resulting DNA with any other length, and any other propanol concentrations. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make

and use the invention commensurate in scope with these claims. The previous rejection over claims 1-3 is maintained for the reasons of record as set forth in the Office action. The rejection over claim 10 is moot due to applicant's cancellation of the said claim. The rejection over claims 22-26 is necessitated by applicant's amendment to the claims.

Factors to be considered in determining whether a disclosure meets the enablement requirement of 35 U.S.C. §112, first paragraph, have been described *In re Wands*, 8 USPQ2d 1400(1988). They are:

1. The breadth of the claims;
2. The nature of the invention;
3. The state of the prior art;
4. The predictability or lack thereof in the art
5. The level of skill in the art;
6. The amount of direction or guidance present;
7. The presence or absence of working examples;
8. The quantity of experimentation needed.

The breadth of the claims

The breadth of the claims seems to encompass all polymerization reactions using any DNA template (with any length), and any *Thermococcus litoralis* DNA polymerase in the presence of 1-propanol with a concentration of between 1%-8% to produce DNA product with any length.

The nature of the invention

The nature of the invention is a method of generating mutations in PCR products (DNA fragments) by adding propanol to the polymerization reaction mixture.

The state of the prior art/ The predictability or lack thereof in the art

The use of 1-propanol in PCR reaction with any Thermococcus litoralis DNA polymerase is unpredictable, as evidenced by applicant's own publication, Claveau et al (DNA and Cell Biology. Vol. 23 (11): 789-795; 2004; cited previously). The Claveau reference states the followings:

"...the enzyme was able to amplify amplicons of 2.8kb. With 8.0% propanol, the longest amplicon obtained was 0.8kb." (p. 793, left col., para 1).

In addition, the instant specification also states: "In presence of 7.0% propanol, the enzyme was able to amplify amplicons of 2.8kb. In presence of 8.0% propanol, the longest amplicon obtained was 0.7kb." (Spec. p.26, lines 1+)

These passages in the reference and the instant specification indicate that the method can only be used to generate products that are no longer than 0.8kb with 8.0% propanol. This also indicates that it is highly unpredictable to use the claimed method to generate DNA fragments with any length.

In the Claveau reference, applicants further state the followings:

"... Deep Vent$_r$® (exo-) did not respond to propanol..." (p.794, left col., para 4).

This passage in the reference indicates that the effect of propanol on various *Thermococcus litoralis* DNA polymerase is also unpredictable.

The level of one of ordinary skill

The level of skill would be high, and most likely at the Ph.D. level..

The amount of direction or guidance present/The presence or absence of working examples

The only guidance presented in the instant specification is directed to PCR amplification reactions using certain percentage of 1-propanol with Vent polymerase (p. 17+ of the spec.) to generate amplicons with certain length such as 0.7kb in the presence of 8% propanol (see Examples of the spec.). The specification does not recite methods of using any Thermococcus litoralis DNA polymerases to generate DNA product with any length. Since the effect of propanol on Thermococcus litoralis DNA polymerases for generating product with any length is unpredictable as discussed supra, detailed guidance should be provided for all the species encompassed in the entire genus of methods.

The quantity of experimentation needed

Due to the unpredictabilities of the effect of propanol on different Thermococcus litoralis DNA polymerases for generation of DNA product with any length, and the lack of guidance in the instant specification, large quantities of experimentation would be required. Since the instant specification only provides guidance for one example of (using propanol with Vent polymerase), undue experimentations must be carried out to practice the entire genus of claimed method.

Conclusion

Therefore based on the evidences as a whole regarding each of the above factors (e.g. factors 1-8), the specification, at the time the application was filed, does not satisfy the enablement requirement for the instant claimed method.

Discussion and Answer to Argument

12. Applicant's arguments have been fully considered but they are not persuasive for the following reasons (in addition to reasons of record). Each point of applicant's traversal is addressed below (applicant's arguments are in italic):

Applicants assert the claim amendment has overcome the previously set forth Scope of Enablement rejection. However, the claim amendments are not sufficient to overcome the previously set forth rejection. Applicants are respectively directed to the above discussion for reasons of the said rejection.

Claim Rejections - 35 USC § 103

13. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

(Note: the instant claim numbers are in bold font.)

14. Claims 1-3 and 22-26 are rejected under 35 U.S.C. 103(a) as being unpatentable over Chevet et al (Nucleic Acids Research. Vol. 23(16): 3343-3344. 1995), and Buchi (Buchi, J. "The Constitution-Effect Relationships from a New Viewpoint" Deutsche Apotheker-Zeitung 1966, pages 1695-1700 (1-29 for English translation)). The previous rejection over claims 1-3 is maintained for the reasons of record as set forth in the Office action. The rejection over claims

10 and 18-21 is moot due to applicant's cancellation of the said claim. The rejection over claims 22-26 is necessitated by applicant's amendment to the claims.

The instant claims recite a method for inducing a random mutation into a nucleic acid sequence comprising the steps of:

Providing a nucleic acid sequence for use as DNA template of between 50 and 50 000 base pair; and

Submitting said DNA template to polymerization reaction with a *Thermococcus litoralis* DNA polymerase mutant, in presence of between 1% to 8% (v/v) of 1-propanol in order to increase polymerase's intrinsic capacity to induce random mutation.

Chevet et al, throughout the reference, teach methods adding various reagents to PCR reactions. The reference teaches using Vent polymerase (i.e. *Thermococcus litoralis* DNA polymerase) (p. 3344, right col., para 2), DNA as template (p. 3343), and ethanol (p. 3344, right col., para 2), which reads on the method of **clms 1** and **3**. The reference also inherently teaches the concentration of ethanol to be between the critical ranges of below 8%, because the reference teaches PCR reaction was carried out in the presence of ethanol and PCR products was formed (p. 3344, right col., para 2). As evidenced by Claveau et al (DNA Cell Biology. Vol. 23(11): 789-795; 2004; cited previously), "...increasing its [alcohol] concentration above 8% resulted in complete inhibition..." (p.793, left col., para 1). Thus, the ethanol concentration used by Chevet for the PCR reaction has to be within the workable range for the reaction to produce products (i.e. non-inhibition of the reaction).

Although the Chevet reference does not explicitly teach the reaction will induce random mutations as recited in the preamble of **clm 1** and **clm 2**, the "random mutation" is an inherent property of the Vent polymerase to induce random mutations including transversion/transition, as evidenced by Keohavong et al (PCR Methods and Applications, Vol 2, 288-292; 1993; cited previously). Thus, the method using Vent polymerase would inherently produce random mutations as recited in **clms 1** and **2**.

The reference also teaches the sizes of the DNA templates used ranging from 593 bp to 15kbp (p.3343, col.1, para 2; Figure 1), which reads on the range of bp recited in **clms 1**, **22** and **23**.

The Chevet reference also does not explicitly teach the reaction is carried out in the presence of propanol (such as 0.1-8%).

However, it would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to substitute propanol (which has one more methylene group than ethanol) for ethanol to produce a homologous reaction mixture for PCR with favorable physicochemical properties (e.g., see MPEP §2144.09 "An obviousness rejection based on similarity in chemical structure and function entails the motivation of one skilled in the art to make a claimed compound, in the expectation that compound similar in structure will have similar properties." In re Payne, 606 F.2d 303, 313, 203 USPQ 245, 254 (CCPA 1979). See In re Papesch, 315 F.2d 381, 137 USPQ 43 (CCPA 1963) (discussed in more detail below) and In re Dillon, 919 F.2d 688, 16 USPQ2d 1897 (Fed. Cir. 1991). Here, Buchi indicates that homologous compounds will lead to "optimal" properties (e.g., see Buchi, section 4.4.3, "the study of homologous series is extremely important for the development of medicines with optimal

properties ... lengthening the alkyl groups causes modification of important physical and chemical properties and chemical reactivity with the receptor, resulting in a gradual change in the activity and type of effect"). Thus, the "optimal" properties exhibited with the ethanol homolog, propanol can improve the PCR reaction through various physico-chemical interactions.

The Chevet reference also does not explicitly teach the alcohol (e.g. propanol) concentration is between 7%-8%. However, as discussed above, the reference inherently teach the PCR reaction is conducted with a propanol concentration of below 8%, because an alcohol concentration above 8% would completely inhibit the PCR reaction (Chevet et al, p.793, left col., para 1). As PCR products are produced in the Chevet reference, the alcohol concentration used in the Chevet reference must be less than 8%. The explicit range of 7%-8% recited in **clms 24-26** is obvious over the reference's range. See MPEP 2144.05. In the case where the claimed ranges "overlap or lie inside ranges disclosed by the prior art" a prima facie case of obviousness exists. In re Wertheim, 541 F.2d 257, 191 USPQ 90 (CCPA 1976).

Discussion and Answer to Argument

15. Applicant's arguments have been fully considered but they are not persuasive for the following reasons (in addition to reasons of record). Each point of applicant's traversal is addressed below (applicant's arguments are in italic):

Applicants argue because "ethanol 'resulted in excessive evaporation'", "substituting ethanol instead of propanol would lead to an unworkable embodiment". (Reply, p.6, para 1). Applicants also argue "Chevet et al. never teach nor suggest replacing ethanol with propanol, and in fact, Claveau et al. indicate that such a replacement is not recommended."

However, the above obviousness rejection is based on the obvious replacement of ethanol with propanol, not a substitution of propanol with ethanol. In addition, applicants have not provided factual evidence to show that using ethanol would lead to non-enabled embodiments. The Claveau reference does not teach that "ethanol" would not work with the claimed invention. In fact, the Claveau reference only teaches "Preliminary experiments showed that adding ethanol resulted in excessive evaporation; thus, investigation with this alcohol were not pursued further". That is the PCR reaction can be conducted in the presence of ethanol, irrespective of its evaporation during or after the reaction. The Claveau reference does not teach that replacing ethanol with propanol in a PCR reaction would not work. As discussed above, the Chevet reference teaches successfully using ethanol in PCR reaction. It is prima facie obvious to replace ethanol with propanol in a PCR reaction due to the chemical similarity between ethanol and propanol, as discussed supra.

New Claim Rejections

Claim Rejections - 35 USC § 112

16. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Scope of Enablement Rejection

17. Claims 11-13 and 17 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for 1-propanol used in PCR reaction with thermo polymerase, $Vent_r^{®}$ with DNA template to generate mutations in DNA with length less than or equal to 0.8kb

in the presence of less than 8% 1-propanol, does not reasonably provide enablement for any other thermo polymerase (such as Deep Vent polymerase), any other DNA template with any other length, any other resulting DNA with any other length, and any other propanol concentrations. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

Factors to be considered in determining whether a disclosure meets the enablement requirement of 35 U.S.C. §112, first paragraph, have been described *In re Wands*, 8 USPQ2d 1400(1988). They are:

1. The breadth of the claims;
2. The nature of the invention;
3. The state of the prior art;
4. The predictability or lack thereof in the art
5. The level of skill in the art;
6. The amount of direction or guidance present;
7. The presence or absence of working examples;
8. The quantity of experimentation needed.

The breadth of the claims / The nature of the invention

The breadth of the claims seems to encompass all polymerization reactions using any DNA template (with any length), and any DNA polymerase in the presence of any alcohol to produce DNA product with any length. The nature of the invention is a method of generating mutations in PCR products (DNA fragments) by adding alcohol to the polymerization reaction mixture.

The state of the prior art / The predictablility or lack thereof in the art

The effect of various alcohol on DNA polymerase reaction using various DNA polymerases are highly unpredictable. It is not know how various alcohol molecules (such as propanol, ethanol, butanol, etc.) affect DNA polymerase reaction. In addition, the ultimate affect of alcohol on various polymerases (Vent, Taq, for examples) would be unpredictable. For example, Claveau et al (DNA and Cell Biology. Vol. 23: 789-795; cited previously) teach using propanol in PCR reactions with various thermo polymerases. The study shows that while PCR reaction with Vent polymerase generated mutations with the addition of propanol in the reaction mixture, reaction with a closely related polymerase (Deep Vent) does not respond to the addition of propanol (See Result and Discussion of the reference). Thus, using propanol in a PCR reaction using Deep Vent would not produce the desired result.

Furthermore, various alcohols would also have different effects on various polymerases. For example, Lu et al (Trends in Genetics. Vol. 9: 297; cited previously) teach a method of adding glycerol (an alcohol) in PCR reaction to improve PCR reaction of Taq polymerase and improve reaction efficiency and specificity (See Figure 1 of the reference). This effect of glycerol would contradict the instant claimed invention that using alcohol to promote mutations in a PCR reaction. Lastly, different templates would also have different effects in the outcome of a PCR reaction. For example, Lu et al teach that certain DNA template could not be amplified (See 2nd paragraph of the reference), and therefore would not allow the generation of mutated PCR products.

Further, the use of 1-propanol in PCR reaction with Taq polymerase would inhibit the polymerization reaction, as evidenced by applicant's own publication. Claveau et al (DNA and Cell Biology. Vol. 23 (11): 789-795; 2004), state the followings:

"Considering the deletion-to-mutation ratio and the low mutation frequency obtained with Taq in the presence of critical propanol concentration, we did not further investigate this condition, considering it unsuitable for error-prone PCR". (emphasis added; p. 791, right col., para 3).

This passage in the reference indicates that Taq polymerase cannot be used for the claimed method of generating mutations with polymerization reaction in the presence of 1-propanol.

The Claveau reference further states the followings:

"...the enzyme was able to amplify amplicons of 2.8kb. With 8.0% propanol, the longest amplicon obtained was 0.8kb." (p. 793, left col., para 1).

This passage in the reference indicates that the method can only be used to generate products that are no longer than 0.8kb with 8.0% propanol. This also indicates that it is highly unpredictable to use the claimed method to generate DNA fragments with any length.

The Claveau reference further states the followings:

"...increasing its concentration above 8% resulted in complete inhibition, indicating that the concentration range providing optimal error-prone PCR conditions is narrow." (p. 793, left col., para 1).

This passage in the reference indicates that only a "narrow" range of concentration of propanol will work with the claimed method. The claimed range of 0.1%-15% as recited in Claim 1 is beyond the critical 8%.

Furthermore, the Claveau reference states the following:

"increasing mutation rate to 10^{-1} error/bp/PCR or above... results in mutant libraries where no active genes are left" (emphasis added; p. 789, right col., right col.).

This passage in the reference indicates that certain mutant nucleic acid sequences cannot be "biologically active protein" as it is claimed in Claim 7 of the instant application. Thus, it is highly unpredictable whether a given mutant nucleic acid will encode for a "biologically active protein".

The level of one of ordinary skill

The level of skill would be high, and most likely at the Ph.D. level..

The amount of direction or guidance present/The presence or absence of working examples

The only guidance presented in the instant specification is directed to PCR amplification reactions using certain percentage of 1-propanol and Taq, or Vent polymerase (p. 17+ of the spec.). The specification does not recite methods of using any polymerases with any alcohol (of any concentration) for generating any DNA product with any length. Since the effect of various alcohol on DNA polymerase reaction is highly unpredictable as discussed supra, detailed guidance should be provided for all the species claimed in the entire genus of the claimed methods.

The quantity of experimentation needed

Due to the unpredictabilities of the effects of various alcohol on different polymerases under different reaction conditions (as discussed supra), and the lack of guidance in the instant specification, large quantities of experimentation would be required. In addition, to achieve mutations, certain alcohol concentrations must be used. Alcohol concentrations that are outside the critical range would inhibit the reaction, as discussed above. Since the instant specification only provides guidance for one example of (using propanol with Vent polymerase), undue experimentations must be carried out to practice the entire genus of claimed method.

Conclusion

Therefore based on the evidences as a whole regarding each of the above factors (e.g. factors 1-8), the specification, at the time the application was filed, does not satisfy the enablement requirement for the instant claimed method.

Second paragraph of 35 U.S.C. 112

18. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

19. Claim 13 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 13 recites the limitation "said protein analogs" in line 1. There is insufficient antecedent basis for this limitation in the claim.

Claim Rejections - 35 USC § 103

20. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

(Note: the instant claim numbers are in bold font.)

21. Claims 11-13 and 17 are rejected under 35 U.S.C. 103(a) as being unpatentable over Chevet et al (Nucleic Acids Research. Vol. 23(16): 3343-3344. 1995), and Buchi (Buchi, J. "The Constitution-Effect Relationships from a New Viewpoint" Deutsche Apotheker-Zeitung 1966, pages 1695-1700 (1-29 for English translation)).

The instant claims recite a method for preparing a library of mutated recombinant nucleic acid sequence comprising the steps of: providing a nucleic acid sequence for use as DNA template: submitting said DNA template to polymerization with at least one DNA polymerase in presence of alcohol in concentration sufficient to lower the fidelity of said DNA polymerase and causing mutagenesis during said polymerization.

Chevet et al, throughout the reference, teach methods adding various reagents to PCR reactions. The reference teaches using Vent polymerase (p. 3344, right col., para 2), DNA as template (p. 3343), and ethanol (p. 3344, right col., para 2), which reads on the method of **clms 11, 12 and 17**. The reference also teaches the amplified DNA is encoding a surface protein (p. 3343, left col., para 2), which reads on the proteins of **clm 13**.

Although the Chevet reference does not explicitly teach the reaction will induce mutations as recited in the preamble of **clms 11, and 17**, the "mutation" induction is an inherent

property of the Vent polymerase to induce random mutations including transversion/transition, as evidenced by Keohavong et al (PCR Methods and Applications, Vol 2, 288-292; 1993). Thus, the method using Vent polymerase would inherently produce mutations as recited in **clms 11, and 17**.

The Chevet reference also does not explicitly teach the reaction is carried out in the presence of propanol (the elected species).

However, it would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to substitute propanol (which has one more methylene group than ethanol) for ethanol to produce a homologous reaction mixture for PCR with favorable physicochemical properties (e.g., see MPEP §2144.09 "An obviousness rejection based on similarity in chemical structure and function entails the motivation of one skilled in the art to make a claimed compound, in the expectation that compound similar in structure will have similar properties." In re Payne, 606 F.2d 303, 313, 203 USPQ 245, 254 (CCPA 1979). See In re Papesch, 315 F.2d 381, 137 USPQ 43 (CCPA 1963) (discussed in more detail below) and In re Dillon, 919 F.2d 688, 16 USPQ2d 1897 (Fed. Cir. 1991). Here, Buchi indicates that homologous compounds will lead to "optimal" properties (e.g., see Buchi, section 4.4.3, "the study of homologous series is extremely important for the development of medicines with optimal properties ... lengthening the alkyl groups causes modification of important physical and chemical properties and chemical reactivity with the receptor, resulting in a gradual change in the activity and type of effect"). Thus, the "optimal" properties exhibited with the ethanol homolog, propanol can improve the PCR reaction through various physico-chemical interactions.

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Sue Liu whose telephone number is 571-272-5539. The examiner can normally be reached on M-F 9am-3pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Doug Schultz can be reached at 571-272-0763. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

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